CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-158

MEDICAL REVIEW



Medical Officer's Review of NDA 21-158

FACTIVE™ (gemifloxacin mesylate)
Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)

Applicant: SmithKline Beecham

Date of submission: December 16, 1999

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Date review completed: December 14, 2000

Abbrevations used in this review:

- ABECB or AECB: Acute Bacterial Exacerbation of Chronic Bronchitis
- FQ(s): Fluoroquinolone(s)
- MRSP: Macrolide-resistant Streptococcus pneumoniae
- PP: per protocol
- PRSP: Penicillin-resistant Streptococcus pneumoniae
- ITT: intent to treat

Background

The following fluoroquinolones (FQs) are indicated for the oral treatment of ABECB:

- Ciprofloxacin (Cipro) 500-750 mg BID x 7 to 14 days.
- Ofloxacin (Floxin) 400 mg BID x 10 days.
- Lomefloxacin (Maxaquin) 400 mg qd x10 days.
- Levofloxacin (Levaquin) 500 mg qd x 7 days.
- Sparfloxacin (Zagam) 400 mg loading dose followed by 200 mg qd for total treatment duration of 10 days.
- Grepafloxacin (Raxar) dosing for ABECB was 400 or 600 mg qd x 10 days prior to withdrawal of the indication.
- Trovafloxacin (Trovan) dosing for ABECB was 100 mg qd x 7-10 days prior to withdrawal of the indication.
- Moxifloxacin (Avelox) 400 mg qd x 5 days
- Gatifloxacin (Tequin) 400 mg qd x 7-10 days

NOTE: A supplemental NDA is pending for Tequin. The applicant will seek approval of a 5-day regimen thereby replacing the currently-labeled, 7-10 day treatment duration.



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The following list includes <u>non-FQ</u> antimicrobials indicated for the treatment of ABECB. Except for cefdinir, all are indicated for 7, 10, or 14 days of treatment. All of listed below are dosed orally with the exception of imipenem-cilastatin.

- Trimethoprim-sulfamethoxazole (Bactrim or Septra) one double strength tablet (160 mg/800mg) BID x 14 days
- Clarithromycin (Biaxin) 250-500 mg BID x 7-14 days
- Cefaclor (Ceclor) 500 mg q 12 hours x 7 days
- Ceftibuten (Cedax) 400 mg qd x 10 days
- Cefuroxime axetil (Ceftin) 250-500 mg BID x 10 days
- Cefprozil (Cefzil) 500 mg q 12 hours x 10 days
- Loracarbef (Lorabid) 400 mg q 12 hours x 7 days
- Cefdinir (Omnicef) 300 mg BID x 5 days
- Imipenem-cilastatin (Primaxin) 500-750 mg IM q 12 hours for at least 2 days after resolution of symptoms
- Cefixime (Suprax) 400 mg qd or 200 mg BID (duration not specified)
- Cefpodoxime (Vantin) 200 mg q 12 hours x 10 days

No anti-infective drug to date has received approval for penicillin- or macrolide-resistant *Streptococcus pneumoniae* in association with the ABECB indication.

As can be seen from the lists above, numerous anti-infective drugs are approved for the treatment of ABECB. There is no lack of alternative treatments for this indication.

SmithKline Beecham's Proposed ABECB Labeling

Clinical Studies

In a study designed to assess the efficacy of *Factive* in AECB, 689 patients received either 320 mg *Factive* (N=351) once daily for 5 days or 500 mg clarithromycin (N=358) twice daily for 7 days. The mean duration of chronic bronchitis in patients was 12 years; approximately 10% of the patients had more than 4 exacerbations of chronic bronchitis that required antibacterial therapy during the year prior to study entry.

The results are shown in the table below.

Efficacy Evaluable			Intent	to Treat
Bacteriological Response at Follow-up	Factive 320 mg daily 5 days	Clarithromycin 500 mg b.i.d. 7 days	Factive 320 mg daily 5 days	Clarithromycin 500 mg b.i.d. 7 days
: Success (%)	86.7	73.1	75.4	63.6
Treatment difference, % [95% CI]	13.6 [-2.0, 29.2]	11.8 [-4.3, 27.9]
Clinical Response at Follow-up				
Success (%)	85.4	84.6	79.5	78.2
Treatment difference, % [95% CI]	0.8 [-5.	0, 6.6]	1.3 [-4.	7, 7.3]

In a prospectively defined analysis of a subset of patients with Haemophilus influenzae identified as a pathogen at screening, treatment with Factive resulted in a faster time to eradication of Haemophilus influenzae from the sputum compared with clarithromycin (p=0.02).

	Treatment Group				
	Factive	Clarithromycin			
	320 mg q.d.	500 mg b.i.d.			
	= H. Inf	Tuenzae Isolated			
Timepoint	N N				
Day 0	. 12	12			
	Persistance of H. Influenzae				
Day I	0	6			
Day 2	0	3			
Day 3	0	3			
Day 4	0	2			
Day 5	0	l l			
Day 6	0				

CLINICAL REVIEW

NOTE: The MO reviewed a randomized 20% subset of patients (this randomized sample was generated by the statistical reviewer). Following review of these patients, the MO concluded that the investigators'/applicant's assessment of evaluability and outcomes were acceptable.

To garner approval for this indication, SB submitted data from six clinical studies (two "principal", one "supportive", three "other") to demonstrate safety and efficacy for ABECB. The two principal studies and the single supportive study were double blind and comparative and utilized 5 days of gemifloxacin. However, the supportive study used the European approved comparator: trovafloxacin 200 mg p.o. q.d. for 5 days. (The FDA-approved trovafloxacin regimen for ABECB was 100 mg p.o. q.d. for 7-10 days. This indication was subsequently withdrawn from U.S. marketing due to liver toxicity concerns.)

The remaining "other" studies utilized either 7 or 10 days duration of gemifloxacin therapy in ABECB. The applicant only seeks approval of the 5 day ABECB regimen. Hence, these studies are not reviewed here.

The protocol numbers and titles follow:

Principal AECB Studies

<u>068</u> "A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 5 days versus oral clarithromycin 500 mg twice daily for 7 days for the treatment of AECB."

<u>070</u> "A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 5 days versus oral amoxicillin/clavulanate 500/125mg three times daily for 7 days for the treatment of AECB."

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Supportive AECB Study

069* "A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 5 days versus oral trovafloxacin 200 mg once daily for 5 days for the treatment of AECB."

NOTE: *Study 069 is a principal study in EU; listed as supportive due to use of EU approved trovafloxacin 200 mg dose for 5 days (unapproved dose in US).

Other AECB Studies

008 "A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 7 days versus oral levofloxacin 500 mg once daily for 7 days for the treatment of AECB."

<u>061</u> "An open, non-comparative, multi-center study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 7 days for the treatment of lower respiratory tract infections (AECB or CAP) in adults."

<u>001</u> "A double-blind, multi-center, parallel group, dose ranging study to compare the efficacy and safety of oral gemifloxacin at doses of 80 mg, 160 mg or 320 mg once daily versus oral ofloxacin 400mg twice daily for 10 days for the treatment of acute bacterial exacerbations of chronic bronchitis."

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Summary information for these studies is included in the following table:

from SB's Table 3.H.14 Gemifloxacin Studies in Acute Exacerbation of Chronic Bronchitis

Study Principal co	<u>Treatment Regimen</u> ntrolled studies	<u>Duration</u>	<u>N*</u>	Geographic Region
068	gemifloxacin 320mg qd Clarithromycin 500mg bid	5 days 7 days	351 361	Europe, US, Canada.
070	gemifloxacin 320mg qd Augmentin 500/125mg tid	5 days 7 days	304 296	Europe
Supportive	study			
069	Gemifloxacin 320mg qd	5 days	303	Europe
	Trovafloxacin 200mg qd	5 days	314	
Other studi	es (7 or 10 days treatment) ·		
008	gemifloxacin 320mg qd	7 days	293	US, Canada
	levofloxacin 500mg qd	7 days	293	
061** (open)	gemifloxacin 320mg qd	7 days	261	World-Wide/ except North America
001 (phase II)	gemifloxacin 320mg qd gemifloxacin 160mg qd gemifloxacin 80mg qd ofloxacin 400mg bid	10 days 10 days 10 days 10 days	64 67 67 69	Europe, North America

^{*} N = number of patients randomized to treatment.

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^{**}Study 061 was conducted in patients with CAP or AECB. Only AECB patients summarized here.

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The "Principal" ABECB Studies

	Study 068	Study 070
Title	A randomized, double-blind, double-	A randomized, double-blind, double-
	dummy, multicenter, parallel group study	dummy, multicenter, parallel group study
	to assess the efficacy and safety of oral	to assess the efficacy and safety of oral
	gemifloxacin 320 mg once daily for 5 days	gemifloxacin 320 mg once daily for 5 days
	versus oral clarithromycin 500 mg twice	versus oral amoxicillin/clavulanate
	daily for 7 days for the treatment of AECB	500/125 mg three times daily for 7 days for the treatment of AECB
Comparators	Clarithromycin	Amoxicillin/clavulanate‡
Study dates	20 November 1998 to 03 June 1999	30 September 1998 to 07 April 1999
Study design	Randomized (1:1), multi-center,	Same as study 068
	double-blind, double-dummy,	
	parallel group	
Countries	Austria, Canada, France, Germany,	Belgium, Denmark, Estonia,
	Mexico, United	Finland, France, Germany, Ireland
	Kingdom, USA*	Norway, Sweden, United
		Kingdom
No. of centers	93	112
Age	>40 y.o.	Same as study 068
Gender	Male and female	Same as study 068
Visits	Visit 1: Day 0	Same as study 068
	Visit 2: Days 2-4	
	Visit 3: Days 9-11 (end-of-therapy visit)	
	Visit 4: Days 14-21 ("test-of-cure" visit)†	
Inclusion	Visit 5: Days 28-35 (long-term follow-up)	Same as study 068
criteria	History of chronic bronchitis	Same as study ooo
Criteria	characterized by cough and	
	sputum production for more than	:
	2 consecutive years and for most	
	days in a consecutive 3-month	
	period.	
Clinical	Success	Same as study 068
responses	• Failure (assessable at visit 3)	_
(primary	Recurrence (assessable at visit 4)	
efficacy	Unable to determine	
parameter)		

^{*}Seventy-three (73) percent of patients enrolled in this study came from the U.S.

[†]Prior to the applicant's decision to break the study blind, the applicant extended this visit window to include visit data between days 13 and 24. Because this decision took place blinded to treatment arm, the MO accepts this post hoc change in the analysis plan.

[‡] Although Augmentin isn't specifically approved for ABECB, per se, it is approved for "lower respiratory tract infections". This is an acceptable comparator.

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Studies 068 and 070 were similar in trial design (with the exception of geographic distribution).

Patient populations defined:

ITT:

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All randomized patients who took at least one dose of study

medication.

Bacteriology ITT: All randomized patients who took at least one dose of study

medication and had at least one pathogen identified at

Screening.

Clinical PP:

This population includes patients who satisfied the

inclusion/exclusion criteria and who subsequently adhered to

the protocol. The clinical PP population is a subset of the ITT

population. (Patients with an outcome of "unable to determine" were excluded from the PP analyses.)

Bacteriology PP:

This population includes patients who satisfied the

inclusion/exclusion criteria, who subsequently adhered to the

protocol and who had at least one pathogen identified at Screening. The bacteriology PP population is a subset of the

bacteriology ITT population.

According to the applicant, the principal efficacy analysis involved the clinical per protocol population. The FDA considers the intent-to-treat population as coprimary.

The applicant prospectively defined non-inferiority where the 95% confidence interval around the difference in cure rates did not extend beyond 10% in favor of the comparator.



Results

Data from both studies are presented concurrently below:

SB's Table 3.H.15 Patient Disposition: AECB Principal Studies 068 and 070

rationt Disposition.		Study 068 Study 070			
	Gemi-	Clarithro-	Gemi-	Amoxicillin/	
	floxacin	mycin	floxacin	clavulanate	
	320mg qd		320mg qd		
	(5 days)	(7 days)	(5 days)	(7 days)	
Population	n	n	n	n	
Randomized	351	361	304	296	
Received Study Medication (ITT)	351	358	304	296	
Total withdrawn, n (%)	40 (11.4)	40 (11.2)	17 (5.6)	21 (7.1)	
Populations for analysis:					
Clinical PP end of therapy	298	304	268	274	
Clinical PP follow-up	287	292	264	266	
Clinical PP long term/follow-up	279	284	250	254	
Bacteriology ITT	57	66	51	49	
Bacteriology PP end of therapy	47	54	44	45	
Bacteriology PP follow-up	45	52	44	44	
Bacteriology PP long term follow-up	44	50	42	42	

The most frequent reasons for withdrawal was adverse events (3.1% and 4.5% for gemifloxacin and clarithromycin, respectively, in study 068; 3.3% and 3.0% for gemifloxacin and Augmentin, respectively, in study 070) and protocol deviations, including drug non-compliance (4.3% and 2.5% for gemifloxacin and clarithromycin, respectively, in study 068; 2.0% and 2.0% for gemifloxacin and Augmentin, respectively, in study 070).

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SB's Table 3.H.16 Demographic and Baseline Characteristics: AECB Principal Studies 068 and 070 (Clinical PP Follow-Up Population)

(0	5	tudy 06	8	. 1	Study 070			
	Ge	mi-	Clar	ithro-	Ge	mi-		xicillin/
	flox	acin	m	ycin	flox	acin		ulanate
Demographic/baseline	320	mg qd	500ı	mg bid	3201	ng qd	-	25mg tid
Characteristic	N=	287	N=	292	N=	264	N	=266
Gender: n (%)								
Male	144	(50.2)	155	(53.1)	141	(53.4)	157	(59.0)
Female	143	(49.8)	137	(46.9)	123	(46.6)	109	(41.0)
Age								
Mean (SD)		(12.0)		2 (11.5)		(11.7)		8 (12.2)
Range	37	- 88	3	9 – 88	4	10-92	4	1-97
Race: n (%)								(0.0.0)
White	240	(83.6)	253	(86.6)	262	(99.2)	263	(98.9)
Black	19	(6.6)	17	(5.8)	0		1	(0.4)
Oriental	2	(0.7)	2	(0.7)	2	(0.8)	1	(0.4)
Other	26	(9.1)	20	(6.8)	0		1	(0.4)
Duration of chronic //								
bronchitis (years)			_				_	
n		287		292		264		66
Mean (SD)		7 (12.2)		9 (11.4)		5 (11.8)		.5 (10.6)
Range	2.0	- 65.1	2.0	- 66.2	1.9	9-78.8	2	.0-58.8
Exacerbations treated with								
antibacterials in last year, n								(0.0)
0	52	(18.1)	54	(18.5)	17	(6.4)	24	(9.0)
1-4	204	(71.1)	208	(71.2)	193	(73.1)	203	(76.3)
>4	29	(10.1)	30	(10.3)	53	(20.1)	39	(14.7)
Unknown	2	(0.7)	0		1	(0.4)	0	
Smoking pack years, n (%)		(====)		(0.0.0)			00	(00.0)
0	60	(20.9)		(22.3)	88	(33.3)	86	(32.3)
>0-30	104			(34.6)	96	(36.4)	103	(38.7)
>30	122			(42.8)	77	(29.2)	73	(27.4)
Unknown	1	(0.3)	1	(0.3)	3	(1.1)	4	(1.5)
Severity of AECB*, n (%)	_		_			(0.4)	•	
Stage 1	0		0	(0.0.0)	1	(0.4)	0	(0.4.0)
Stage 2		(97.2)		(96.2)	238			(94.0)
Stage 3	8	- (2.8)	11	(3.8)	25	(9.5)	16	(6.0)

^{*} According to published severity criteria

Demographic characteristics were equally balanced between treatment arms for both studies.

SB's Table 3.H.17 Number (%) of Patients with Key Pathogens Associated with AECB at Screening: Principal AECB Studies 068 and 070

	_	Study 00	<u>88</u>		<u>Study 070</u>		
	G	emi-	Cla	rithro-	Gemi-	Amox	icillin/
	Flo	xacin	m	ycin	floxacin		ılanate
Bacteriology Population	320	mg qd	500	mg bid	320mg qd	500/1	25mg tid
PP Follow-Up	N	=45	N	=52	N=44	N	=44
M. catarrhalis	16	(35.6)	18	(34.6)	14 (31.8)	13	(29.5)
H. influenzae	7	(15.6)	6	(11.5)	12 (27.3)	6	(13.6)
S. pneumoniae	5	(11.1)	7	(13.5)	7 (15.9)	9	(20.5)
H. parainfluenzae	8	(17.8)	5	(9.6)	2 (4.5)	0	in request of the light section of the light
ITT .		N=57		N=66	N=51	N	I= 4 9
M. catarrhalis	20	(35.1)	18	(27.3)	16 (31.4)	13	(26.5)
H. influenzae	9	(15.8)	7	(10.6)	13 (25.5)	8	(16.3)
S. pneumoniae	8	(14.0)	8	(12.1)	9 (17.6)	10	(20.4)
H. parainfluenzae	8	(14.0)	6	(9.1)	2 (3.9)	0	

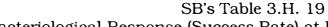
At baseline, the primary pathogens were equally represented between study groups. However, a greater overall proportion of *M. catarrhalis* was seen in both study arms than one might anticipate. This appears to be a chance occurrence.

SB's Table 3.H.18 Clinical Response (Success Rate) at Follow-Up (Test of Cure): Principal AECB Studies

	Gemifloxacin % (n/N)	Comparator % (n/N)	Treatment Difference % (95% CI)
CLINICAL RESPONSE AT	FOLLOW-UP (PRI	MARY PARAMET	ER)
Clinical PP Population			
068	85.4 (245/287)	84.6 (247/292)	0.8 (-5.0, 6.6)
070	93.6 (247/264)	93.2 (248/266)	0.3 (-3.9, 4.6)
ITT Population	•		
068	79.5 (279/351)	78.2 (280/358)	1.3 (-4.7, 7.3)
070	88.5 (269/304)	88.9 (263/296)	-0.4 (-5.4, 4 <i>.</i> 7)

With regard to clinical efficacy, the applicant demonstrated non-inferiority (delta <10%) in studies 068 and 070, independently, in both clinical PP and ITT populations.





Bacteriological Response (Success Rate) at Follow-Up (Test of Cure):

Principal AECB Studies

	I Interpar Auces	Ottudics	
	Gemifloxacin	Comparator	Treatment Difference
	% (n/N)	% (n/N)	% (95% CI)
BACTERIOLOGICAL RESPONS	E AT FOLLOW-UP		
Bacteriology PP Population			
068	86.7 (39/45)	73.1 (38/52)	13.6 (-2.0, 29.2)
070	90.9 (40/44)	79.5 (35/44)	11.4 (-3.3, 26.0)
Bacteriology ITT Population			
068	75.4 (43/57)	63.6 (42/66)	11.8 (-4.3, 27.9)
070	82.4 (42/51)	75.5 (37/49)	6.8 (-9.1, 22.8)
_			

Similar bacteriologic efficacy results were seen between gemifloxacin and comparator group.

Bacteriologic efficacy per pathogen is discussed below.

Conclusion:

Gemifloxacin is effective in the treatment of ABECB utilizing a dosage regimen of 320 mg p.o. q.d. x 5 days.

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Study 069

Although the applicant demonstrated efficacy from the two principal studies, the MO also reviewed supportive study 069 for the purpose of assessing gemifloxacin's clinical activity against specific pathogens in ABECB.

Title	group study to assess the effica mg once daily for 5 days versu for 5 days for the treatment of	A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily for 5 days versus oral trovafloxacin 200 mg once daily for 5 days for the treatment of AECB.				
Study dates	25 September 1998 - 10 M					
Study design	Randomized (1:1), multi-	center, double-blind, double-				
•.	dummy, parallel group	dummy, parallel group				
Countries	Austria, Belgium, France, Germany, the Netherlands,					
	Poland, Switzerland, United Kingdom					
No. of centers	100	100				
Age	≥40 y.o.	>40 y.o.				
Gender	Male and female					
Visits	Protocol	Post hoc blinded revisiont				
	Visit 1: Day 0	Visit 1: Days –2 to 0				
	Visit 2: Days 2-4	Visit 2: Days 6-10				
	Visit 3: Days 7-9	Visit 3: Days 11-22 = test-of-cure				
	Visit 4: Days Days 12-19	Visit 4: Days 23-36				
	Visit 5: Days 26-33					
Inclusion	History of chronic brone	hitis characterized by cough and				
criteria	sputum production for 2	or more consecutive years and				
	for most days in a conse	cutive 3-month period.				

†Prior to the applicant's decision to break the study blind, the applicant modified visit windows. Because this decision took place blinded to treatment arm, the MO accepts this post hoc change in the analysis plan.

Patient Disposition: Study 069

	Treatme	nt Group
	Gemifloxacin 320mg qd	Trovafloxacin 200mg qd
Population	n	n
Randomized	303	314
Received Study Medication (ITT)	302	314
Total withdrawn, n (%)	15 (5%)	31 (10%)
Completed Study	287	283
Clinical PP End of Therapy	277	283
Clinical PP Follow-Up	272	275
Clinical PP Long-Term Follow-Up	262	258
Bacteriology ITT	55	58
Bacteriology PP End of Therapy	55	53
Bacteriology PP Follow-Up	53	51
Bacteriology PP Long-Term Follow-Up	50	45

More patients withdrew from the trovafloxacin treatment arm than the gemifloxacin arm due to adverse events and study non-compliance.

Demographic Characteristics (Clinical PP Follow-Up Population)

		Treatmen	t Group	
Demographic Characteristic	320n	loxacin ng qd 272	Trovafloxacin 200mg qd N=275	
Gender, n (%)				
Male	164	(60.3)	169	(61.5)
Female	108	(39.7)	106	(38.5)
Age (yr)	•			
Mean (SD)	60.9	(10.8)	62.3	(10.7)
Range	39	39 - 91		- 89
Race, n (%)				
White	- 269	(98.9)	271	(98.5)
Black	1	(0.4)	0	
Oriental	2	(0.7)	4	(1.5)
Weight (kg)				· · · · ·
Mean (SD)	73.3	(15.3)	75.1	(16.6)
Range	30	- 128	41	- 168
Height (cm)				
Mean (SD)	167.	.1 (8.6)	167	.6 (9.0)
Range	144	l - 190	141	l - 195

The demographics were equally represented between study arms.

SB's Table 3.H.20 Number (%) of Patients with Key Pathogens Associated with AECB at Screening: AECB Supportive Study 069

Bacteriology PP Follow-Up		lloxacin 0 mg qd 53	Trovaflo 200 m N=5	g qđ
H. influenzae	21	(39.6)	18	(35.3)
M. catarrhalis	11	(20.8)	9	(17.6)
H. parainfluenzae	9	(17.0)	12	(23.5)
S. pneumoniae	5	(9.4)	11	(21.6)

Unlike the principal studies 068 and 070, the major baseline pathogen was H. influenzae — as one would expect.

SB's Table 3.H.21 Clinical and Bacteriological Response at Follow-Up (Test of Cure): Supportive AECB Study 069

	% (n/N)	Success Rate Trovafloxacin % (n/N)	Treatment Difference % (95% CI)
CLINICAL RESPONSE (PRIMARY Clinical PP Population ITT Population	91.5 (249/272)	87.6 (241/275) 83.1 (261/314)	3.9 (-1.2,9.0) 6.3 (0.9, 11.7)
BACTERIOLOGICAL RESPONSE Bacteriology PP Population Bacteriology ITT Population	86.8 (46/53) 83.6 (46/55)	82.4 (42/51) 74.1 (43/58)	4.4 (-9.4,18.3) 9.5 (-5.4, 24.4)

Gemifloxacin clinical and microbiologic success rates were consistent with those seen in principal studies 068 and 070.

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Bacteriologic Efficacy by Pathogen

Although the MO concluded that gemifloxacin was effective in the treatment of ABECB, the reviewer must now address whether sufficient data are presented to support the applicant's requested pathogens for this indication: *H. influenzae*, *M catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and

SB's Table 3.H.22
Pre-Therapy Pathogens Eradicated or Presumed Eradicated at
End of Therapy and Follow-Up:
AECB Combined Studies 068, 070 and 069

·.	Bacteriology PP**			Ī	Bacterio	logy ITT		
	Gemiflo	xacin	All Compa		Gemiflo		All Com	
Follow-Up	N=1	42	N=14	17	N=1	63	N=1	173
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	148/169	(87.6)	136/171	(79.5)	154/194	(79.4)	144/198	(72.7)
H. influenzae	45/49	(91.8)	36/42	(85.7)	47/55	(85.5)	36/46	(78.3)
M catarrhalis	29/30	(96.7)	23/28	(82.1)	30/34	(88.2)	23/30	(76.7)
S. pneumoniae	15/20	(75.0)	21/25	(84.0)	15/23	(65.2)	23/28	(82.1)
H. parainfluenzae	16/18	(88.9)	16/18	(88.9)	17/20	(85.0)	17/22	(77.3)
	The second secon		MENORARY AND INC.					

End of Therapy	N=1	46	N=15	52	N=1	63	N=1	73
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	164/175	(93.7)	153/176	(86.9)	173/194	(89.2)	162/198	(81.8)
H. influenzae	49/51	(96.1)	40/45	(88.9)	51/55	(92.7)	40/46	(87.0)
M catarrhalis	32/32	(100.0)	26/29	(89.7)	33/34	(97.1)	26/30	(86.7)
S. pneumoniae	19/21	(90.5)	23/25	(92.0)	20/23	(87.0)	25/28	(89.3)
H. parainfluenzae	16/18	(88.9)	16/18	(88.9)	17/20	(85.0)	17/22	(77.3)
	CONTRACTOR AND INVESTIGATION OF THE PROPERTY OF	والمتحالة	era vitoria personalità caraga reconstrucció	Committee and the second sections of the second	Market Broken (1994), St. C. M. Birgings and Application of the Control of the Co	TO STATE STATE STATE OF THE STA	on the second and a second	CHICAN THE CONTRACTOR SHOP

Note: failures at end of therapy were carried forward into the follow-up analysis by applying the following algorithms: (1) All failures and 'unable to determines' at end of therapy are added to the denominator at follow-up

(2) For PP populations, successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.

• n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.

** Bacteriology PP population at end of therapy or follow-up.

With special attention to the Bacteriology Per Protocol population at follow up, the MO concludes that sufficient gemifloxacin efficacy data were submitted to support labeling claims for *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and *H. parainfluenzae* in ABECB. However, insufficient gemifloxacin experience (at the requested 320 mg p.o. q.d. x 5 days dosing) was submitted to support a labeling claim for : _____ Indeed, the numerically lower efficacy rates seen for gemifloxacin relative to comparator imply that gemifloxacin may be less effective.

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NDA 21-158
Factive (gemifloxacin mesylate)
MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

With regard to assessing the applicant's proposed PRSP and MRSP efficacy claims:

There is insufficient evidence at present to conclude that PRSP in ABECB poses a public health problem that merits a labeling claim for PRSP. In addition, prior to considering such a claim for ABECB, the applicant should establish evidence of clinical efficacy in a more serious indication (e.g., community-acquired pneumonia).

Similarly, the applicant has not submitted sufficient evidence to warrant the approval of an out-of-class resistance claim for MRSP at the present time for several reasons:

- 1. Macrolides are not the most important therapeutic option for the treatment of serious pneumococcal infections.
- 2. Based upon the current scientific literature, penicillin resistance represents the more important public health problem with regard to drug-resistant *Streptococcus pneumoniae*.
- 3. If in the future an out-of-class resistance claim for MRSP is scientifically warranted, then additional data supporting the efficacy of gemifloxacin in the treatment of pneumococcal infections within a specific serious indication is recommended, including clinical experience in severe disease (including bacteremia) due to *S. pneumoniae* (and MRSP).

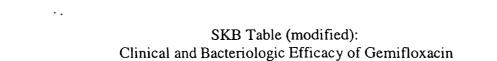
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The following two summary tables reiterate the data presented above for studies 068, 069, and 070. Namely, in most analyses, at both the follow-up (test-of-cure) and long-term follow-up visits, gemifloxacin was non-inferior to clarithromycin, Augmentin, and trovafloxacin (non-FDA approved dosing) in the treatment of ABECB.

SKB Table (modified): Clinical and Bacteriologic Efficacy of Gemifloxacin Relative to Comparators at the <u>Test-of-Cure Visit</u>

Clinical Success	s: Per Protocol Population	on	
	Gemifloxacin	Comparator	Treatment Difference (95% CI)
068	85.4% (245/287)	84.6% (247/292)	0.8% (-5.0, 6.6)
069	91.5% (249/272)	87.6% (241/275)	3.9% (-1.2,9.0)
070	93.6% (247/264)	93.2% (248/266)	0.3% (-3.9, 4.6)
Clinical Succes	s: Intent-to-Treat Popul	ation	
068	79.5% (279/351)	78.2% (280/358)	1.3% (-4.7, 7.3)
069	89.4% (270/302)	83.1% (261/314)	6.3% (0.9, 11.7)
070	88.5% (269/304)	88.9% (263/296)	-0.4% (-5.4, 4.7)
Bacteriological	Success: Per Protocol P	Population	
068	86.7% (39/45)	73.1% (38/52)	13.6% (-2.0, 29.2)
069	86.8% (46/53)	82.4% (42/51)	4.4% (-9.4,18.3)
070	90.9% (40/44)	79.5% (35/44)	11.4% (-3.3, 26.0)
Bacteriological	Success: Intent-to-Trea	at Population	
068	75.4% (43/57)	63.6% (42/66)	11.8% (-4.3, 27.9)
069	83.6% (46/55)	74.1% (43/58)	9.5% (-5.4, 24.4)
070	82.4% (42/51)	75.5% (37/49)	6.8% (-9.1, 22.8)



Clinical Success	s: Per Protocol Population	on	
	Gemifloxacin	Comparator	Treatment Difference (95% CI)
068	79.6% (222/279)	78.5% (223/284)	1.0% (-5.7, 7,8)
069	82.4% (216/262)	76.4% (197/258)	6.1% (-0.8, 13.0)
070	87.2% (218/250)	87.4% (222/254)	-0.2% (-6.0, 5.6)
Clinical Succes	s: Intent-to-Treat Popul	ation	
068	74.6% (262/351)	72.3% (259/358)	2.3% (-4.2, 8.8)
069	80.5% (243/302)	70.4% (221/314)	10.1% (3.3., 16.8)
070	83.2% (253/304)	81.8% (242/296)	1.5% (-4.6, 7.5)
Bacteriological	Success: Per Protocol P	opulation •	
068	81.8% (36/44)	62.0% (31/50)	19.8% (2.2, 37.5)
069	68.0% (34/50)	68.9% (31/45)	-0.9% (-19.6, 17.8)
070	81.0% (34/42)	76.2% (32/42)	4.8% (-12,8, 22,3)
Bacteriologica	l Success: Intent-to-Trea	nt Population	
068	71.9% (41/57)	56.1% (37/66)	15.9% (-0.8, 32.6)
069	63.6% (35/55)	58.6% (34/58)	5.0% (-12.9, 23.0)
070	74.5% (38/51)	69.4% (34/49)	5.1% (-12.5, 22.7)

Relative to Comparators at the Long-Term Follow-Up Visit

As stated previously, the MO concludes that the applicant has demonstrated clinical and bacteriologic efficacy for gemifloxacin in the treatment of ABECB.



Time to Eradication of Haemophilus influenzae

The applicant seeks a labeling claim for gemifloxacin's faster time to eradication of *H. influenzae* compared to clarithromycin. (See proposed Clinical Studies section above.)

A subset of the patient population (100 patients were originally planned) from study 068, at 30 specified sites, were enrolled in an analysis of the bacterial eradication of *Haemophilus influenzae*. (This component was not included in study 070.)

The following centers participated in the eradication study:

Canada:

062, 069, 070, 071

Mexico:

002,003

UK:

195, 196

USA:

009, 015, 023, 029, 030, 034, 040, 046, 050, 051, 505, 506,

517, 564, 572, 574, 577

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Each patient brought their first morning sputum samples to the clinic daily between Day 1 through 6. The sample was supposed to be refrigerated immediately after collection and then transported to the clinic.

According to the protocol: "Each patient will then bring the sample, in the provided transport container, to the site within two hours (and absolutely no longer than four hours) after collecting the sample. All sputum samples generated by patients participating in the bacterial eradication analysis will be sent (within two hours of receipt by the site) to a certified local laboratory for Gram staining and routine culture. All isolates will be sent to the central laboratory."

In addition, the analysis plan stated:

Bacterial Eradication Analysis

This analysis is restricted to the subset of patients taking part in the bacterial eradication analysis who are identified as having the *H. influenzae* pathogen at Screening (Day 0).

The *H. influenzae* bacteriological outcome on Days 1-6 of therapy will be categorized as follows:

Bactérial eradication: The elimination of the *H. influenzae* pathogen from the repeat sputum culture

Bacteriological persistence: The presence of the *H. influenzae* pathogen in the repeat sputum culture

Unable to determine: An assessment of bacteriological outcome could not be made

Kaplan-Meier plots of times to *H. influenzae* eradication will be presented and the time to bacterial eradication of *H. influenzae* will be compared.

The proportion of patients who have a *H. influenzae* bacteriological outcome of "bacterial eradication" on Day 1 will be compared between treatment groups using the Fisher's exact test. Two-sided 95% confidence intervals will be calculated for the difference in proportions between the treatment groups.

For each patient, the time to bacterial eradication will be defined as the time in days to the first outcome of bacterial eradication. Patients who have an outcome of 'unable to determine' will be censored at that timepoint.

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Results

Although 100 patients were originally planned, due to lower than expected isolation for *H. influenzae*, enrollment was increased and 193 patients were studied. Of this cohort only 24 patients (12 in each group) were identified with *H. influenzae* at baseline. Twelve (12) subjects out of the 24 included in this substudy came from center 195. The remaining 29 center supplied the remaining 12 subjects. (Note: Center 195 enrolled a total of 20 subjects into Study 068.)

The applicant submitted the following table:

SB's Table 3.H.23
Number (%) of Patients with Response of Bacterial Persistence by
Day (Bacterial Eradication Population):
Principal AECB Study 068

	Gemifloxacin // 320mg qd // N=12		Clarithromycin 500mg bid N=12		
Timepoint	n	(%)	n	(%)	
Day 0	12	(100.0)	12	(100.0)	
Day 1	0	(0)	6	(50.0)	
Day 2	0	(O)	3	(25.0)	
Day 3	O	(O)	3	(25.0)	
Day 4	O	(O)	$\ddot{2}$	(16.7)	
Day 5	О	(0)	1	(8.3)	
Day 6	0	(0)	ī	(8.3)	

Note: According to the applicant, the bacteriological outcome of eradication did not include 5 patients who were assigned an outcome of unable to determine, as a sputum sample could not be obtained.

According to the applicant: "With regard to the bacterial eradication analysis of *H. influenzae*, a statistically significant difference (P=0.02) was noted between treatment groups for the time to bacterial eradication of *H. influenzae* isolated at screening, with a shorter time to eradication noted in the gemifloxacin group compared to the clarithromycin group; the median time to eradication was one day for patients in the gemifloxacin group and two days for patients in the clarithromycin group."

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Karen Higgins, Statistical Reviewer, provided the following table:

Day H. influenzae cleared from sputum	Gemifloxacin N = 12	Clarithromycin N = 12
Day I	7	3
Day 2	4	4
Day 3	0	1
Day 4	0	0

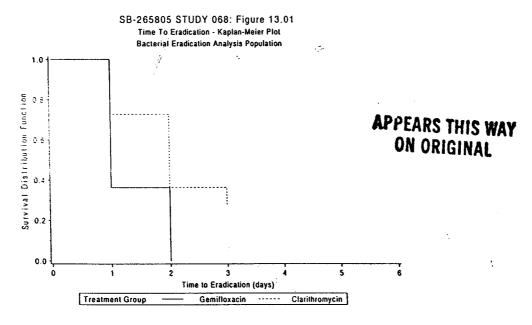
1 subject was censored on day 0

1 subject was censored on day 0

1 subject was censored on day 3

2 subject was censored on day 4

The applicant submitted the following Kaplan-Meier plot addressing time to eradication for *H. influenzae*:



Very little information was submitted in the original NDA to support this claim. Hence, the MO contacted the applicant and asked them to identify the centers and patients who participated in this study. In addition, the MO asked the applicant whether correlation could be demonstrated between time to eradication and clinical success. In response, the applicant submitted the following data:

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C	Clinical Outcome, b	y Visit
	Gemifloxacin	Clarithromycin
	End of Therapy (F	EOT)
Success	8	10
Failure	2	2
UTD	2	0
	Follow-up (FU	J)
Success	8	8
Recurrence	0	2
Lo	ong-Term Follow-u	p (LTF)
Success	6	7
Recurrence	2	1

UTD= Unable to determine

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Similarly, the clinical outcomes of these subjects were as follows.

Clinical Cure Rate	Gemifloxacin	Clarithromycin
PP at EOT	. 8/10 (80%)	10/12 (83%)
PP at follow-up	8/10 (80%)	8/12 (67%)
ITT at EOT	8/12 (67%)	10/12 (83%)
ITT at follow-up	8/12 (67%)	8/12 (67%)
ITT at long-term follow-up	6/12 (50%)	7/12 (58%)

The applicant explained:

"Clinical outcome at end of therapy, follow-up, and long-term follow-up appear similar for the two treatment groups. However, examination of the clinical evaluation data at an earlier timepoint, the on-therapy visit, indicates that more gemifloxacin-treated patients than clarithromycin-treated patients have improvements in dyspnea, decreases in sputum volume, and decreases in sputum purulence. Differences between the treatment groups for these assessments are less apparent by the end of therapy and follow-up visits."

The MO agrees that time to H. influenzae eradication may possibly be enhanced with gemifloxacin therapy compared to clarithromycin. However, because clinical outcome is the primary efficacy parameter in this condition, the applicant has presented limited information to support this quality of life claim. Ultimately, at the test of cure visit, it doesn't appear that enhanced time to eradication translates into better clinical outcomes. Although two recurrences were noted at the follow-up visit for the clarithromycin arm and none for gemifloxacin, there were also two "unable to determine" patients at the end-of-therapy visit who were censored from subsequent analyses. Furthermore,

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because a single investigator out of 30 centers supplied 50% of the cases, bias is a concern.

Based on the data submitted, the MO concludes that this labeling claim should not be granted.

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<u>Safety</u>

As is discussed elsewhere (see Dr. John Power's ABECB safety review), significant gemifloxacin safety concerns persist with regard to rash/sensitization and possible liver toxicity. QT effects are also present but do not appear to differ significantly from that seen with other FDA-approved FQs (e.g., gatifloxacin and moxifloxacin).

Recommendation:

Although efficacy has been demonstrated for Factive in the treatment of ABECB at a dose of 320 mg p.o. q.d. x 5 days, pending further assessment of the safety concerns mentioned above, the MO recommends that ABECB should <u>not</u> be approved at this time.

Assuming this NDA is approvable in the future, based on the current data submitted, the ABECB indication should include the following pathogens: *H. influenzae*, *M catarrhalis*, *S. pneumoniae*, and *H. parainfluenzae*. As discussed above, should not be approved.

Brad Leissa, MD
Medical Team Leader/HFD-590

NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

Medical Officer's Review NDA 21-158 Factive Resubmission CAP Indication

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EXECUTIVE SUMMARY Medical Officer's Review of NDA 21-158 (resubmission) FACTIVE (gemifloxacin mesylate 320 mg tablets)

Applicant's Proposed Indication:

Factive is indicated for the treatment of Community-acquired pneumonia caused by Streptococcus pneumoniae (including penicillin-, clarithromycin- and cefuroxime-
resistant strains), Haemophilus influenzae; Moraxella catarrhalis;-Mycoplasma pneumoniae; Chlamydia pneumoniae;
The proposed dose is one 320-mg tablet daily for 7 days.

Background:

DA 21-158 was originally submitted by GlaxoSmithKline as a new drug application	a
NDA) dated December 15, 1999. In that application, the applicant requested the	
dications of community-acquired pneumonia, acute exacerbation of chronic bacteria	al
onchitis,	

A not approvable letter was issued on December 11, 2000 wherein the applicant was informed that there was insufficient information about the drug to determine whether the product was safe for use under the conditions suggested in its proposed labeling. The applicant was also informed that based on a review of the clinical trial data submitted, it was concluded that gemifloxacin was effective in treating community-acquired pneumonia (CAP) of mild to moderate severity. In order to obtain a serious disease claim, it was suggested that additional studies be conducted in patients who meet accepted standardized criteria. Additionally, to obtain labeling that highlights the role of gemifloxacin in the treatment of PRSP in CAP additional PRSP isolates were necessary as well as additional clinical trial experience in the treatment of patients with severe CAP due to *Streptococcus pneumoniae* (including cases of bacteremic pneumococcal pneumonia).

Clinical Studies:

Efficacy:

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Six clinical studies were performed to demonstrate the efficacy of gemifloxacin in CAP. Four of the studies were controlled (three of a double-blind design and one an open study) and two studies were uncontrolled. Five studies are complete and one, study 287, is ongoing.

Table 1
Community Acquired Pneumonia: Controlled and Uncontrolled
Studies of Gemifloxacin

	Studies of C	Gemifloxacin		
Study	Treatment Regimen	Duration	N*	Geographic Region
Controlle	ed studies			
011	gemifloxacin 320 mg od amoxicillin /clavulanate 1g/125 mg tid		168 156	Europe, S. Africa
012	gemifloxacin 320 mg od cefuroxime 500 mg /clarithromycin 500 mg bid	7 or 14 days 7 or 14 days	319 322	U.S. Canada, Europe, S. Africa
049	gemifloxacin 320 mg od trovafloxacin 200 mg od		290 281	U.S., Mexico, Spain
185	gemifloxacin 320 mg od IV ceftriaxone 2g od + oral cefuroxime 500 mg bid**	1-7 days +	172 173	Australia, Europe, Guatemala, Lebanon, Philippines, Singapore and North America
Uncontro	lled studies			
061	gemifloxacin 320 mg od	7 days	216 [§]	World-Wide (Except N. America)
287	gemifloxacin 320 mg od	7 days	188	Asia, U.S., Mexico Philippines

^{*} N refers to the number of randomized patients (enrolled for uncontrolled studies)

A total of 1349 patients received treatment with gemifloxacin 320 mg once daily and 927 patients received treatment with an active comparator.

In the four randomized, controlled studies (Studies 011, 012, 049 and 185), 947 patients were treated with gemifloxacin and 927 received a comparator. Four hundred two (402) patients received treatment with gemifloxacin 320 mg once daily in the uncontrolled studies.

The **primary efficacy endpoint** in the four controlled clinical studies (Studies 011, 012, 049, and 185) and in uncontrolled Study 061, was clinical response at the follow-up or test of cure [TOC] visit in the per protocol (PP) population. In non-comparative study 287, the primary objective was to demonstrate bacteriological efficacy in the treatment of CAP of suspected pneumococcal origin and so the primary endpoint in this study was the

^{**} both comparator treatments were administered with or without macrolide

[§] Study 061 was conducted in patients with CAP or AECB. N= number of patients with CAP.

bacteriological response at the follow-up visit in the bacteriologic ITT (intent-to treat) population.

An analysis of clinical success rates at follow-up for the CPP and ITT populations are presented below for each study. The results of study 011 show that the clinical efficacy of gemifloxacin at follow-up was at least as good as (non-inferior to) the comparator regimen of amoxicillin/clavulanate in both the clinical per protocol and the ITT populations since the lower limit of the 95% CI exceeded the pre-specified non-inferiority margin of -15%. The results for the 7 – 14 day comparative studies and 7-day fixed uncontrolled studies supported this conclusion.

Table 2
Clinical Success at Follow-Up
CAP Controlled and Uncontrolled Studies 011, 012, 049, 185, 061 and 287

	Success Rate					
	Gemifloxacin	Comparator*	Treatment Difference			
	% (n/N)	% (n/N)	% (95% CI)**			
	Clinical PP Po	pulation				
Controlled Studies						
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)			
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)			
Study 049	94.0% (202/215)	89.9% (186/207)	4.1 (-1.1, 9.3)			
Study 185	92.2% (107/116)	93.4% (113/121)	-1.15 (-7.73, 5.43)			
Pooled 011/012/049/185 [§]	90.5% (631/697)	91.1% (636/698)	-0.34 (-4.70, 4.02)			
Uncontrolled Studies		` ,	(,)			
Study 061	91.7% (154/168)	-	(86.1, 95.2)			
Study 287	89.8% (132/147)	-	(84.9, 94.7)			
	Intent-to-T	reat				
Controlled Studies						
Study 011	77.2% (129/167)	79.1% (121/153)	-1.8 (-10.9, 7.2)			
Study 012	78.4% (250/319)	84.7% (272/321)	-6.4(-12.4, -0.4)			
Study 049	87.5% (253/289)	81.1% (227/280)	6.5 (0.5, 12.4)			
Study 185	75.6% (130/172)	78.6% (136/173)	-3.03 (-11.89, 5.83)			
Pooled 011/012/049/185§	80.5% (762/947)	81.6 (756/927)	-1.02 (-7.44, 5.39)			
Uncontrolled Studies		•	` , ,			
Study 061	82.9% (179/216)	-	(77.0, 87.5)			
Study 287	78.5% (146/186)	-	(72.6, 84.4)			

In an independent FDA analysis where clinical response at TOC was assessed by age, race, and gender as well as by study and duration of treatment, similar results were obtained.

The clinical efficacy of gemifloxacin was supported by similar bacteriological success rates for gemifloxacin treated patients in all studies.

In the BPP follow-up population, 88.5% (461/521) of initial pathogens in the combined gemifloxacin group were either eradicated or presumed eradicated as compared with 89.9% (301/335) of initial pathogens in the combined comparator group. By pathogen eradication rates can be seen in the table below. Eradication rates at follow-up for these pathogens in the BITT population were slightly lower in both combined treatment groups.

Streptococcus pneumoniae and Mycoplasma pneumoniae, the most frequently isolated pathogens in this combined study population of CAP patients, had eradication rates in the gemifloxacin group of 90.7% and 88.7%, respectively (BPP population). For the pooled comparator group the corresponding rates for these pathogens were 92.9% and 87% respectively.

Table 3
Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up
CAP Combined Principal and Supportive Studies 012, 049, 011, 185 and 287, 061

	Combined CAP studies 012, 049, 011, 061, 185, 287							
			ogy PP**				ology ITT	
	Gemifl	oxacin	All Com	parators	Gemifl			parators
Follow-Up	N=415		N=274		N=552		N=355	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	461/521	(88.5)	301/335	(89.9)	552/702	(78.6)	361/445	(81.1)
гМ. pneumoniae	102/115	(88.7)	94/108	(87.0)	126/153	(82.4)	109/129	(84.5)
S. pneumoniae	117/129	(90.7)	65/70	(92.9)	136/168	(81.0)	76/94	(80.9)
C. pneumoniae	51/54	(94.4)	41/45	(91.1)	62/77	(80.5)	48/59	(81.4)
H. influenzae	51/58	(87.9)	25/28	(89.3)	60/75	(80.0)	30/37	(81.1)
programa two species								*
M. catarrhalis	13/14	(92.9)	3/3	(100.0)	15/16	(93.8)	4/4	(100.0)
K. pneumoniae	17/19	(89.5)	4/4	(100.0)	23/29	(79.3)	4/4	(100.0)

Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:

An independent FDA analysis of pathogen eradication rates in subjects treated for 7 days by study revealed similar rates to those above, independent if patients were enrolled in the 7 day studies (011, 061, and 287) or if they received 7 days of treatment in the studies where a 7 or 14 day treatment regimen could have been utilized.

In summary, the data presented in the CAP studies in both the original NDA 21-158 submission and the currently under review resubmission provide sufficient evidence of the efficacy for gemifloxacin in the treatment of CAP (of mild to moderate severity) due to Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, and Chlamydia pneumoniae with a labeled duration of therapy of 7 days.

⁽¹⁾ failures and 'unable to determines' at end of therapy are added to the denominator at follow-up

⁽²⁾ successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.

^{*} n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.

^{**} Bacteriology PP follow-up population.

Special Populations:

There was no evidence that age or gender had any effect on the clinical response to gemifloxacin. As the majority of patients were white (91.7% of gemifloxacin patients). Clinical success rates for the small number of black, oriental and other race patients did not indicate any differential responses compared with the overall study population but the numbers of subjects was too small to allow for valid comparisons.

Specific to the resubmission, the applicant reassessed response to treatment by duration of treatment, by severity of disease, by hospitalization studies and by the presence or not of bacteremia.

Duration of Treatment:

The applicant provided analyses of clinical response by duration of treatment. Subjects were divided by the applicant into those that received 7 days or less of treatment and those that received between 8 and 14 days of treatment. The decision to extend the duration of treatment was not made at the time of randomisation but at the On-Therapy visit, thus introducing an element of bias. As per the applicant, the 14-day group results were artificially inflated and the 7-day results deflated in comparison to the 14-day group. Comparisons therefore between the 7- and 14-day groups of the same treatment arm should not be made.

From the Agency's standpoint, it could only be assumed that the investigator would have more often extended the treatment of more ill patients to 14 days, while less ill patients would be given only 7 days. When looking at demographics and baseline characteristics, it was noted that patients in the 14-day group were a few years older on average and that as the severity of disease increased, a larger proportion of subjects received 14 days of treatment.

In the Agency analysis, when the allowed comparisons between treatment groups are made, for both the 7-day fixed and the 7-14 day studies gemifloxacin clinical success rates were similar to those of the respective comparators.

Table 4
FDA Analysis of Clinical Response at Follow-up by Duration of Therapy

	Treatment Group			
	Gemifloxacin n/N (%)	Comparators n/N (%)		
Clinical Per Protocol Population				
7-day Fixed studies*				
Controlled (011)	102/115 (88.7)	99/113 (87.6)		
Uncontrolled (061, 287)	286/315 (90.8)))/113 (07.0)		
Combined (Controlled and Uncontrolled)	388/430 (90.2)			
"7 - 14" day studies**	()			
7 days	329/363 (90.6)	319/348 (91.7)		
14 days†	200/219 (91.3)	218/237 (92.0)		
All patients	529/582 (90.9)	537/585 (91.8)		
Intent-to-Treat Population				
7-day Fixed studies*				
Controlled (011)	129/167 (77.2)	121/153 (79.1)		
Uncontrolled (061, 287)	325/363 (90.6)	(,,,,,,)		
Combined (Controlled and Uncontrolled)	454/569 (79.8)			
"7 - 14" day studies**				
7 days	375/468 (80.2)	371/457 (81.2)		
14 days†	258/312 (82.7)	264/317 (83.3)		
All patients	633/780 (81.2)	636/774 (82.0)		
* includes Studies 011 061 and 287	· · · · · · · · · · · · · · · · · · ·	123.77. (92.0)		

includes Studies 011, 061, and 287

Severity of Disease:

The Fine criteria were retrospectively applied as an indicator of severity of illness in all studies except study 287 where they were applied prospectively. Overall, of the 1012 subjects in the CPP gemifloxacin-treated population, 91 (9.9%) were classified as having severe disease (Fine classes IV and V). Similarly, of the 1349 gemifloxacin ITT patients, 129 (9.5%) had severe disease. Of note however, of the 129 "severe" ITT gemifloxacin subjects, only 4 had class V disease and 125 had class IV disease. Of the 91 PP subjects with severe disease, 89 had class IV disease and 2 had class V disease. The mortality risk for class IV subjects ranges from 9-12%, whereas for class V subjects it is in the 30% range.

The applicant provided demographic statistics on all subjects by degree of severity. This information was requested in order to ascertain if demographic differences could justify the varied success rates between the treatment groups. Most subjects had mild disease (997 gemifloxacin, 656 comparator). On the gemifloxacin arm, there were more females than males and 679 (68%) of the subjects were white, 152 (15%) were oriental and 111

^{**} includes Studies 012, 049, and 185 - all were controlled studies

[†] note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

(11%) were categorized as other. On the comparator arm, patients were predominately white (88%) and there were more males than females. Of note was the mean age of this category of patients, 45-46 years. Those subjects with moderate and severe disease were predominately males on both treatment arms (67-72%), white (73-92%) and significantly older with a mean age of 69 for the moderately ill gemifloxacin-treated subjects (70 comparator), and a mean age of 76 for the severe group of gemifloxacin-treated subjects (comparator, 74).

Clinical response rates for CPP severe CAP patients treated with gemifloxacin, were higher that those seen for patients classified as having mild to moderate disease. However, the ITT analysis was the opposite with the severely ill patients having the lower response rates. The demographics of the ITT population, justify these results in the ITT population, with higher clinical success rates in subjects with mild disease and a mean age of 46 and lower rates in the more elderly subjects classified as having moderate or sever disease. Nevertheless, the success rates are very similar despite the demographic differences.

In the FDA analysis when clinical response at the TOC was assessed in the FDA analysis by duration of treatment and by study, the 7-day treatment patients had similar results to the 14-day treatment patients. Although there wasn't that great a difference in success rates, the rates for the "7 day only subjects" were consistently a little lower than the "other studies". Thus, there potentially may be a trend in patients with more severe CAP (bacteremic, hospitalized, severe Fine score) towards longer durations of treatment. Overall, this data indicated that the data currently available on severe patients is inadequate to support an approval in this group.

Table 5
FDA Analysis of Clinical Response at Follow-up for Severe Patients by Duration of
Therapy

·
nparators /N (%)
(,,,
11 (90.9)
(>0.>)
26 (84.6)
30 (83.3)
56 (83.9)
(33.13)
7.70
16 (81.3)
10 (01.0)
36 (72.2)
43 (69.8)
79 (70.9)

^{*} includes Studies 011, 061, and 287

The clinical review team requested that the applicant provide tables of risk class specific mortality for all ITT patients and for in- and outpatients separately. Overall mortality was similar between the gemifloxacin and comparator-treated groups as well as between the gemifloxacin controlled and uncontrolled study patients with 12 deaths (1.3%) in the gemifloxacin controlled study patients, 13 deaths (1.4%) in the comparator-treated patients, and 5 deaths (1.2%) in the gemifloxacin-treated uncontrolled study patients. There were 17 deaths (1.3%) in all gemifloxacin-treated patients.

When mortality was assessed in the ITT population by in or outpatient status, it was apparent that most of the deaths occurred in the inpatients with 14 of 17 gemifloxacin deaths in inpatients (11 controlled and 3 uncontrolled) as compared to 12 of 13 deaths on the comparators arm.

When deaths were assessed by Fine class, it appeared that mortality rates for Class I, II, and III patients mortality rates were consistent with what was expected based on the

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^{**} includes Studies 012, 049, and 185 - all were controlled studies

[†] note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

publication by Fine et al. 1 In class IV subjects the mortality rates in the clinical studies appeared to be somewhat less than what was reported for Fine Class IV patients. There were too few class V subjects in the dataset to draw any conclusions for this class. (The mortality risk for class IV subjects ranges from 9-12%, whereas for class V subjects it is in the 30% range in the publication by Fine et al.)

The MO concluded that severe disease should not be added to the label for the following reasons:

- The small number of patients with Fine classes IV and V disease (9.9%).
- The lack of additional indicators of the effectiveness of gemifloxacin in severe disease.
- The quality of the data in this submission as compared to those in previous NDAs. Most notably, in NDAs 20-634/20-635 (Levofloxacin), 25.8% of the patients (72/279) studies in to controlled trials had severe disease where severe disease was defined as those subjects with hypotension (diastolic BP < 60 mm Hg in the absence of volume depletion), subjects with mental status changes, subjects who required mechanical ventilation, subjects with bacteremia, and subjects with a baseline RR of > 28/min.
- The lack of an adequate number of cases of CAP etiologically associated with pathogens that would qualify as severe disease.

PRSP:

Regarding penicillin-resistant *Streptococcus pneumoniae* (PRSP), there were 12 evaluable patients with 13 isolates of PRSP treated with gemifloxacin in the combined CPP population of the all studies dataset. All 12 patients with PRSP were both clinical and bacteriological successes at follow-up: i.e. 100% success. All but one of the PRSP patients received treatment for 7 days. There were 2 subjects in this group with severe disease as well as 2 with bacteremia (one with severe disease). 8 of the PRSP subjects were hospitalized. 37 subjects were bacteremic with *Streptococcus pneumoniae*. 11 of the patients with PRSP also had cefuroxime and TMP-SMX-resistant isolates. 10 of these isolates were also resistant to macrolides.

The MO determined that the data gathered by the applicant regarding PRSP was impressive and although it did not meet the standard set by the data that formed the basis for approval for levofloxacin and PRSP, it was adequate to allow for the recommendation of an approval in mild to moderate disease.

¹ Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

MRSP:

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The applicant presented data on 36 BITT gemifloxacin-treated MRSP patients of whom 25 in the BPP populations. There were 14 BITT comparator-treated subjects of whom 12 were in the BPP and CPP populations.

Of the 25 BPP gemifloxacin MRSP, 10 (40%) were also PRSP (11/36 BITT, 30%). All subjects with PRSP and MRSP were clinical successes with presumed eradication at follow-up. 8 had mild disease, one had moderate disease and 1 had severe disease. 3 PP MRSP subjects were bacteremic of whom 2 had mild disease and 1 had severe disease. All 3 were successfully treated with presumed eradication. Of note, there were 2 PP subjects with moderate disease and the remaining subjects were classified as mild or in the cases of the subjects from the original submission, as not severe.

Overall clinical success and bacteriologic success rates on the gemifloxacin arm were 22/25 (88%) for the PP population. For the MRSP ITT gemifloxacin-treated population, there were 27/36 (78%) clinical successes, 4 failures and 5 "unable to determine". Similar results were obtained for the BITT population, with 3 isolates presumed persistent and 6 "unable to determine". Overall clinical and bacteriological success rate on the comparators arm was 11/12 (91.6%). 3 of the 12 BPP subjects were also PRSP.

The MO elected to defer a recommendation for or against an approval for MRSP pending presentation of the application to an Advisory Committee. Issues to be discussed include the fact that typically, approximately 60% of PRSP are also MRSP and approximately 40% of MRSP isolates are also PRSP and the non-issuance of an approval for one isolate should lead to a similar decision for the other. Beyond this however, is the issue of whether an approval should be issued for MRSP. This claim has not been previously granted and scientific issues regarding CAP caused by MRSP as a separate entity remain in question. This issue was presented to an DAIDP Advisory Committee on January 8, 2003. The committee did not discuss the merits of the existence of this indication as a separate entity although they did recommend an approval for CAP due to MRSP for telithromycin.

At the March 4, 2003 DAIDP AC, the issue of MDRSP (multi-drug resistant *Streptococcus pneumoniae*) was discussed. It was the committee's determination that penicillin resistant, macrolide resistant, and cefuroxime-resistant *Streptococcus pneumoniae* are not separate entities but the same and that an approval could be granted for MDRSP and not for each separately.

Cefuroxime-resistant Streptococcus pneumoniae:

In the combined CAP gemifloxacin group (BPP population) there were

• 18 patients with Streptococcus pneumoniae resistant to cefuroxime with an MIC of ≥ 4 ug/mL.

- 12 of the 18 cefuroxime-resistant isolates were also penicillin resistant (3 with an MIC of 4 mcg/mL and 9 with an MIC of 2 mcg/mL).
- 15 of the 18 cefuroxime-resistant isolates were also clarithromycin resistant (10 with MICs of 16 mcg/mL or >, 1 with an MIC of 4 mcg/mL, 3 with an MIC of 3 and 1 with an MIC of 1
- 4 subjects had severe disease, 3 had moderate disease, and 11 had mild disease.
- 2 severe subjects were bacteremic. One subject with mild disease was also bacteremic.

Clinical success and bacteriological eradication/presumed eradication rates at follow-up for the BPP population with cefuroxime-resistant isolates of *Streptococcus pneumonia*e were 17/18 (94.4%). The failure was in a subject with mild disease who was not bacteremic but was hospitalized. This subjects isolate was clarithromycin-resistant (MIC 2 mcg/mL) but penicillin sensitive (MIC 1 mcg/mL).

On the comparators arm there were 7 subjects with *Streptococcus pneumoniae* isolates (PP) resistant to cefuroxime that were all successfully treated (ITT 8). 4 of these isolates were also penicillin-resistant and 5 were also clarithromycin resistant. 2 subjects had severe disease, 1 had moderate disease, and 4 had mild disease. 3 subjects were bacteremic including 1 with severe disease and 2 with mild disease.

MDRSP (Multidrug resistant Streptococcus pneumoniae):

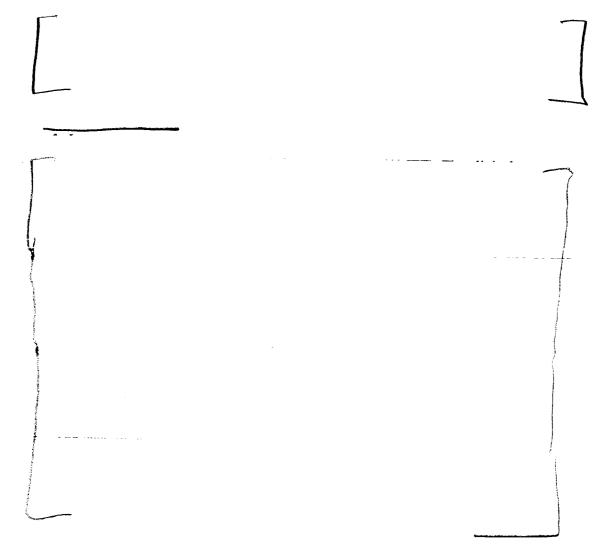
The applicant submitted additional line listings for review on 3/20/03. A review of the listings revealed that there were 9 patients with *Streptococcus pneumoniae* isolates resistant to 4 drugs (penicillin, cefuroxime, macrolides, and TMP-SMX. There were 5 subjects with isolates resistant to 3 drugs including 3 subjects with isolates resistant to penicillin. Two of these 3 were also cefuroxime and TMP-SMX resistant and 1 was also cefuroxime and macrolide resistant. There were 2 subjects with MDR isolates but both of these had isolates that were penicillin sensitive but cefuroxime, clarithromycin and TMP-SMX resistant. Finally there were 5 subjects with isolates resistant to 2 drugs. 3 of these were resistant to clarithromycin and TMP-SMX, 1 was resistant to cefuroxime and TMP-SMX, and 1 was resistant to cefuroxime and clarithromycin. The applicant did not supply data regarding tetracycline-resistant isolates.

Klebsiella pneumoniae:

There were 29 subjects with Klebsiella pneumoniae in the gemifloxacin ITT dataset. Of these, 27 had Klebsiella isolated from the sputum alone, one was of unknown source, and one patient had Klebsiella from the blood and sputum. 17 subjects had Klebsiella alone, 5 had Klebsiella in association with Streptococcus pneumoniae, 5 had Klebsiella associated with other Gram (-) rods, 5 also had or only had Klebsiella associated with Chlamydia or Mycoplasma pneumoniae, and 1 had Klebsiella with Staphylococcus aureus. Twenty-six of 29 (90%) subjects were classified as clinical successes at the follow-up visit and 23/29 (79%) were classified as bacteriologic successes at the follow-up visit. 16/17 (94%)

ITT subjects with *Klebsiella pneumoniae* only were clinical successes and 14/17 (82%) were bacteriologic successes.

There were 22 subjects with Klebsiella pneumoniae included in the BPP population. Of these patients, 2 had severe disease, 4 had moderate disease, and the remaining 16 had mild disease. 22/22 (100%) were clinical successes and 20/22 (90.9%) were bacteriologic successes. Both failures were subjects with mild disease, one hospitalized, one not and Klebsiella was the only pathogen isolated in both. 4 subjects had Klebsiella pneumoniae and Streptococcus pneumoniae (all successes, 3 mild, 1 severe), and 3 had other Gram (-) pathogens isolated concurrently in the sputum (all mild, all successes). All moderately and severely ill subjects were hospitalized, as were 7 of the mild subjects of whom only 1 was a failure. There were 14 BPP subjects with Klebsiella pneumoniae alone with a clinical success rate of 100% and a bacteriologic success rate of 12/14 (85.7%). 10 of the PP subjects had mild diseases, 3 had moderate disease, and 1 had severe disease.



MOR of NDA 21-158 Resubmission/CAP	16
Moraxella catarrhalis and	
Included in the resubmission were efficacy data on 14 isolates of <i>Moraxella catarrhal</i> and 19 isolates of	is
Similar efficacy was found on the comparators arm with and eradication rate of 15/16 Moraxella catarrhalis, and 16/23 (69.6%) for	for
The MO elected to include <i>Moraxella catarrhalis</i> in the CAP indication, given the relatively high eradication rate achieved by gemifloxacin versus this pathogen.	

Conclusions and Recommendations:

In summary, the data presented in the CAP studies in NDA 21-158 provided sufficient evidence of the efficacy for gemifloxacin in the treatment of CAP (of mild to moderate severity) due to Streptococcus pneumoniae (including penicillin-resistant strains), Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Moraxella catarrhalis, with a labeled duration of therapy of 7 days.

Medical Officer's Review of NDA 21-158 FACTIVE (gemifloxacin mesylate 320 mg tablets)

IDENTIFYING INFORMATION

NDA Submission number: 21-158

Applicant: LG LifeSciences Ltd.

25th Floor, LG Twin Tower east 20 Yoido-dong, Youngdungpo-gu

Seoul 150-721, Korea

Contact person: Parexel International

195 West St.

Waltham, MA 02451

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Date of Submission: October 4, 2002 CDER stamp date: October 4, 2002

Date submission received by reviewer: October 9, 2002

Date Review Begun: October 10, 2002

Date Review Completed:

Established name: Gemifloxacin mesylate

Proposed proprietary name: FactiveTM

Chemical name: (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-1-pyrrolidinyl) cyclopropoyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

methanesulfonate

Chemical structure:

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Molecular formula: C₁₈H₂₀FN₅O₄ CH₄O₃S

Molecular weight: 485.49 as mesylate salt

Pharmacologic category: Fluoroquinolone

Dosage Form: Tablets

Route of Administration: Oral

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Strength: 320 mg

Related Drugs:

SB-265805

LB 20304a

IND (oral, tablet)
IND (injection)

Proposed Indications in NDA 21-185:

Acute Bacterial Exacerbation of Chronic Bronchitis Community-Acquired Pneumonia

Applicant's Proposed Labeling:

INDICATIONS AND USAGE

Factive is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute bacterial exacerbations of chronic bronchitis caused by Streptococcus pneumoniae; Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis.

Community-acquired pneumonia caused by Streptococcus pneumoniae (including penicillin-, clarithromycin- and cefuroxime-resistant strains), Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis;-Mycoplasma pneumoniae; Chlamydia pneumoniae: